

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MLC1397.1M	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/GB2004/002604	International filing date (day/month/year) 18.06.2004	Priority date (day/month/year) 18.06.2003
International Patent Classification (IPC) or national classification and IPC G01N33/569, G01N33/68, A61K31/185, A61P33/06		
Applicant MEDICAL RESEARCH COUNCIL et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 13.12.2004	Date of completion of this report 30.06.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399- 8547 Döpfer, K-P	



**INTERNATIONAL PRELIMINARY REPORT
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-28 as originally filed

Sequence listings part of the description, Pages

1-20 received on 29.10.2004 with letter of 25.10.2004

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1/11-11/11 as originally filed

- ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
- * If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 16
- because:
- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☒ no international search report has been established for the said claims Nos. 16
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
 - ☐ See separate sheet for further details

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12
	No: Claims	13-15
Inventive step (IS)	Yes: Claims	1-12
	No: Claims	13-15
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☒ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☒ received by this Authority as an amendment on
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

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Re Item I

Basis of the report

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No International Search Report has been drawn up for the subject-matter of present claim 16. According to Rule 66(1)(e) PCT no International Preliminary Examination is being carried out for the subject-matter of this claim.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

- D1: PIZARRO J C ET AL: "Crystal Structure of a Fab Complex Formed with PfMSP1-19, the C-terminal Fragment of Merozoite Surface Protein 1 from Plasmodium falciparum: A Malaria Vaccine Candidate" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 328, no. 5, 16 May 2003 (2003-05-16), pages 1091-1103, XP004454238 ISSN: 0022-2836
- D2: URQUIZA M ET AL: "Identification of Plasmodium falciparum MSP-1 peptides able to bind to human red blood cells." PARASITE IMMUNOLOGY. OCT 1996, vol. 18, no. 10, October 1996 (1996-10), pages 515-526, XP002304993 ISSN: 0141-9838
- D3: BENJAMIN P A ET AL: "Antigenic and sequence diversity at the C-terminus of the merozoite surface protein-1 from rodent malaria isolates, and the binding of protective monoclonal antibodies." MOLECULAR AND BIOCHEMICAL PARASITOLOGY. 30 NOV 1999, vol. 104, no. 2, 30 November 1999 (1999-11-30), pages 147-156, XP002304994 ISSN: 0166-6851
- D4: NIKODEM D ET AL: "Identification of a novel antigenic domain of Plasmodium falciparum merozoite surface protein-1 that specifically binds to human erythrocytes and inhibits parasite invasion, in vitro." MOLECULAR

- AND BIOCHEMICAL PARASITOLOGY. 30 APR 2000, vol. 108, no. 1, 30 April 2000 (2000-04-30), pages 79-91, XP002304995 ISSN: 0166-6851
- D5: EPP C ET AL: "Expression and purification of Plasmodium falciparum MSP-142: A malaria vaccine candidate" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS, ELSEVIER SCIENCE PUBLISHERS, NL, vol. 786, no. 1-2, 25 March 2003 (2003-03-25), pages 61-72, XP004414354 ISSN: 1570-0232
- D6: FLECK SUZANNE L ET AL: "Suramin and suramin analogues inhibit merozoite surface protein-1 secondary processing and erythrocyte invasion by the malaria parasite Plasmodium falciparum." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 28 NOV 2003, vol. 278, no. 48, 28 November 2003 (2003-11-28), pages 47670-47677, XP002304996 ISSN: 0021-9258
- D7: EP-A-0 486 809 (ERBA CARLO SPA) 27 May 1992 (1992-05-27)

2. Novelty and Inventive Step (Article 33(2)(3) PCT)

- 2.1 The present application addresses a screening method for compounds binding to the merozoite surface protein 1₄₂ (MSP-1₄₂) or fragments thereof, pharmaceutical compositions comprising compounds identified by the above mentioned method; the use of suramin or an analogue thereof for the preparation of an anti-malarial medicament, a pharmaceutical composition comprising suramin.
- 2.2 The screening method comprises contacting a test (or candidate) substance and a comparison substance (e.g. suramin or an analogue) having binding activity for MSP-1₄₂ with MSP-1₄₂ or a fragment thereof (e.g. MSP-1₁₉ or MSP-1₃₃) and determining the amount of test/comparison substance bound to MSP-1₄₂ (or to a fragment thereof).

A screening method having the characteristics as described is not disclosed in the prior art.

The documents of the cited prior art D1 to D4 address attempts to find vaccines against malarial infections which are based on their binding properties to MSP-1 fragments (D5 has been cited for information purposes concerning MSP-1₄₂). Antibodies are preferred as binding agents which shall block the ability of the merozoites either to attach to the surface of erythrocytes or to prevent the merozoite invasion into RBCs. The documents deal with different fragments of

MSP-1 including the 42-kD C-terminal protein and its proteolytic processing products. They are silent with respect to the use of comparison substances with known binding activities for MSP-1₄₂. In fact, none of the documents addresses a screening method for substances of any chemical class which are able to bind to MSP-1₄₂ or its fragments.

The subject-matter of present claims 1-12 is thus novel.

Claim 15 is directed to a pharmaceutical composition comprising an active ingredient identified by a method of claims 1-12 (a type of a so-called "reach-through claim"). The screening method could result in a substance already known as a medicament, i.e. a pharmaceutical composition comprising this known substance would neither be novel. Due to this uncertainty, claim 15 cannot be considered as novel.

Claims 13 and 14 address the second medical use of suramin and a pharmaceutical composition comprising suramin as anti-malarial. This subject-matter is not novel in view of D6 (see claims 1 and 2) which discloses suramin and a composition for the treatment of cerebral malaria.

Any of the documents D1 to D4 can be regarded as closest prior art. The problem underlying the present application can be considered as to provide a method for identifying further anti-malarial compounds targeting an MSP-1 entity. The solution is the screening method with the comparison compound with a known binding affinity to MSP-1₄₂. The prior art is silent with respect to such a method. It does not even suggest to test candidate compounds against a given standard (e.g. suramin, which has not been known before as a binding ligand for MSP-1₄₂). It is possible by means of this method not only to identify whether a candidate compound binds to MSP-1₄₂ or a fragment thereof. It is also possible to give an at least semi-quantitative prediction concerning the anti-malarial activity in comparison to the given standard. This advantage could not be derived from the teachings of the prior art. Thus, inventive step can be acknowledged for present claims 1-12.

Re Item VIII

Certain observations on the international application

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1. Present claim 15 addresses a pharmaceutical composition which refers to claim 10. Claim 10 relates to a screening method, i.e. this reference renders the scope of the claim unclear, since "*a pharmaceutical composition according to a method of claim 10*" lacks clarity of the technical features (Article 6 PCT).